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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,913	05/25/2001	Gustav Gaudernack	1702.401600	7022

5514 7590 12/05/2002

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,913	GAUDERNACK ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-57* is/are pending in the application.

4a) Of the above claim(s) *38 and 44-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-37 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *27-57* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with** traverse of Group I (Claims 27-37) drawn to a peptide (SEQ ID NO: 2) and pharmaceutical compositions in Paper No. 11 (15 October 2002) is acknowledged. The Applicant's argument is found persuasive in terms of rejoining Groups I (claims 27-37) and Group III (claims 39-43). The Applicant's argument is not found persuasive in regards to additional SEQ ID NO's due the search burden associated with additional sequences. Therefore, Groups I and III are hereby rejoined. The remainder of the restriction requirement is still deemed proper and is therefore made FINAL. Claims 38 and 44-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Claims 27-37 and 39-43 will be examined to the extent that they read on a method for vaccinating a human patient using SEQ ID NO: 2.

Status of Application, Amendments, and/or Claims

2. Claims 38 and 44-57 are withdrawn from consideration as discussed above and claims 27-37 and 39-43 are under examination.

3. The Preliminary Amendments of Paper No. 6 (21 May 2001) and Paper No. 7 (25 May 2001) have been entered in full. Claims 1-27 have been cancelled and claims 27-57 have been added.

4. To aid in correlating any papers for this application, all correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Priority

5. The effective US filing date for this application (09/674913) is 30 April 1999 based on PCT/NO99/00141. The priority date for this application (09/674913) is 8 May 1998 based on foreign priority claim to NORWAY 19982098.

Title

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

7. The following title is suggested: ALZHEIMER'S DISEASE VACCINE

Specification

8. The Specification is objected to because of the following informalities: "deposites" is misspelled (pp. 12 line 2). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 27-37 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 27 is directed to a peptide for use in the treatment of Alzheimer's disease or Down's syndrome. Claim 28 is directed to the peptide according to claim 27, wherein the peptide contains a total of 8-25 amino acid residues. Claim 29 is directed to the peptide according to claim 27, wherein the peptide contains a total of 9-20 amino acid residues. Claim 30 is directed to the peptide according to claim 27, wherein the peptide contains a total of 9-16 amino acid residues. Claim 31 is directed to the peptide according to claim 27, wherein the peptide contains a total of 8-12 amino acid residues. Claim 32 is directed to the peptide according to claim 27, wherein the peptide contains a total of 20-25 amino acid residues. Claim 33 is directed to the peptide according to claim 27, wherein the peptide contains a total of 9 amino acid residues. Claim 34 is directed to the peptide according to claim 27, wherein the peptide contains a total of 12 amino acid residues. Claim 35 is directed to the peptide according to claim 27, wherein the peptide contains a total of 13 amino acid residues. Claim 36 is directed to the peptide according to claim 27, wherein the peptide comprises SEQ ID NO: 2 and a fragment thereof. Claim 37 is directed to a pharmaceutical composition comprising SEQ ID NO: 2 and a pharmaceutically acceptable carrier or diluent. Claim 39 is directed to the use of a peptide according to claim 27 for the preparation of a pharmaceutical composition for the treatment or prophylaxis of Alzheimer's disease or for the treatment of Down's syndrome. Claim 40 is directed to a method for vaccinating a human patient disposed to developing, or afflicted with, Alzheimer's disease. Claim 41 is directed to a method for vaccinating a human patient disposed to developing, or

Claim 43 is directed to method according to claim 42, wherein the amount of at least one peptide is in the range of 1 microgram to 1 milligram for each administration.

10. The specification teaches that Alzheimer's disease and Down syndrome patients, intracellular and extracellular deposits of proteins in tangles, neurophil threads, and neuritic plaques are correlated with neuronal dysfunction leading to dementia. These protein deposits have been shown to contain forms of β amyloid precursor protein (βAPP) and ubiquitin-B (Ubi-B) that are aberrant in the carboxyl terminus. These aberrant protein sequences are results of frameshift mutations which probably occur at the transcriptional level or by posttranscriptional editing of RNA.

11. The art teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments in with an immunogenic adjuvant is able to reduce β-amyloid levels within the brains of mice which are transgenic for PDAPP. These mice exhibit Alzheimer type over production and build up of β - amyloid within the brain. However, as recognized in the art, these mice do not exhibit Alzheimer's disease as in humans or plaque morphology and components which are the same as in humans, Alzheimer's disease, Down's Syndrome or other amyloidogenic diseases, see in particular Schenk et al., Nature, 400:173-77, 1999, Games et al., Nature 373(6514): 523-7, 1995 and Chen et al., Progress in Br. Res., 117:327-34, 1998.

12. Thus the claimed invention is directed to a mutant βAPP or Ubi-B peptide, which is not supported by the teachings of the specification or the prior art. One skilled in this art would be expected to reasonably doubt that the claimed invention would work due to the following obstacles: Specific biological actions/activities that the antigenic mutant Aβ peptide or Ubi-B would effect; How does the immunogenic effect relate to symptoms of Alzheimer's disease or

Down's syndrome; Expectation of that Aβ peptide or Ubi-B would be actively involved in either disease (Terry et al., 1994; WO 01/42306). The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

13. Regarding, mutants, fragments, and peptides, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition see in particular Skolnick et al. (2000). For example, Jobling et al. (1991) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted.

14. While general guidance is given in the specification on the synthesis of SEQ ID NO: 2, no working examples are given re: vaccination of subjects using SEQ ID NO: 2, fragments of SEQ ID NO: 2, or a T-cell specific immune response elicited by SEQ ID NO: 2.

15. Thus the claimed invention is directed using a mutant βAPP or Ubi-B peptide to vaccinate a human patient disposed to developing, or afflicted with, Alzheimer's disease or Down's syndrome, which is not supported by the teachings of the specification or the prior art (Tennent et al., 1995; Monsonego et al., 2001). One skilled in this art would be expected to

reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that the antigenic composition of Aβ peptide or Ubi-B would effect; How does the immunogenic effects relate to symptoms of Alzheimer's disease or Down's syndrome; Expectation of that Aβ peptide would be actively involved in amyloid deposition, as opposed to being a non-dynamic component (USPT 5851996; USPT 5780587). The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

16. Regarding specific T-cell immune response, the art recognizes that immune responses include two large branches, humoral and cellular. Due to the large quantity of experimentation necessary to evaluate all the possible aspects of cellular immune responses, the lack of direction/guidance presented in the specification to which aspects of the immune response are most relevant, the absence of working examples directed to all aspects of cellular immune responses, the complex nature of the invention, the unpredictability of the effects of antigens on the mammalian immune system (Chapman, 2000; Frenkel et al., 1999; Frenkel et al., 1998; Frenkel et al., 2000; Friedland et al., 1997; Grubeck-Loebenstein et al., 2000), and the breadth of the claims which fail to recite limitations for which aspects of a mammalian immune response are activated, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Regarding the ancillary effects of the introduction of an immune response in a mammalian nervous system, the specification must establish that the antigens injected into the subjects produce a specific immune response and do not act as pyrogens (leading to cranial

swelling for example). Due to the large quantity of experimentation necessary to evaluate all the effects of the difficulty of predicating an immune response in the nervous system, the lack of direction/guidance presented in the specification about collateral damage due to a vigorous immune response in an immunological privileged area (such as the nervous system), the absence of working examples directed to successful antigen presentation of a neurological protein, the complex nature of the invention, the unpredictability of the effects of antigens on the mammalian nervous system (Elan press releases; USPN 598883; WO 95/32731; WO 99/58552; DeMattos et al., 2001), and the breadth of the claims which fail to recite limitations for what constitutes a successful, controlled immune response in the mammalian brain, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

18. Concerning β-amyloid (Aβ) and fragments thereof, Tanaka et al. (1998) demonstrates that administration of β-amyloid (1-40) into the cerebral ventricle of rats produces learning and memory deficits accompanied by dysfunction in the cholingergic and dopaminergic systems (Abstract). Therefore, instead of eliciting a salubrious immune response to alleviate Alzheimer's disease the administration of the β-amyloid protein or fragments thereof can lead to detrimental neurological effects.

19. Finally, the application must establish a nexus between the specific T-cell immune response recited in the claims for Alzheimer's disease or Down's syndrome and the alleviation of said disease state recited in the claims. In this case, the skilled artisan is not guided as to how a T-cell immune response must affect one or more activates of each targeted peptide (βAPP or Ubi-B) such that the immune response would be determined to be one that alleviates Alzheimer's disease or Down's syndrome. Also, mutant βAPP's are varied and it is not clear that these

peptides would be sufficiently involved in a rate-limiting step for Alzheimer's disease or Down's syndrome such that it could be used in a to elicit a specific and sufficient immune response to slow or prevent the deposition plaque material thereby providing relief from said disorder (Small et al., 2001; Chapman, 2000; Esiri, 2001; Younkin, 2001; Tennent et al., 1995; USPT 5958684; WO 01/42306; WO 97/12992).

20. Claim 39 is rejected under 35 U.S.C. 112, second paragraph because claim 39 provides for the use of a peptide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

21. Claim 39 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Summary

22. Claims 27-37 and 39-43 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
November 20th, 2002